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71479 U.S. PTO 04/30/98

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	P4947US-WO-A
First Inventor or Application Identifier	Buser
Title	TREATMENT OF INFLAMMATORY BOWEL DISEASE USING ORAL DOSAGE....
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

ADDRESS TO: Assistant Commissioner for Patents, Box Patent Application, Washington, DC 20231

1. [X] * Fee Transmittal Form (e.g., PTO/SB/17) (Submit an original and a duplicate for fee processing)
2. [X] Specification [Total Pages 19]
   (preferred arrangement set forth below)
   - Descriptive title of the Invention
   - Cross References to Related Applications
   - Statement Regarding Fed sponsored R & D
   - Reference to Microfiche Appendix
   - Background of the Invention
   - Brief Summary of the Invention
   - Brief Description of the Drawings (if filed)
   - Detailed Description
   - Claim(s)
   - Abstract of the Disclosure
3. [ ] Drawing(s) (35 U.S.C. 113) [Total Sheets]
4. Oath or Declaration [Total Pages]
   a. [ ] Newly executed (original or copy)
   b. [X] Copy from a prior application (37 C.F.R. § 1.63(d)) (for continuation/divisional with Box 17 completed) [Note Box 5 below]
      i. [ ] DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).
5. [X] Incorporation By Reference (useable if Box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.
6. [ ] Microfiche Computer Program (Appendix)
7. Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
   a. [ ] Computer Readable Copy
   b. [ ] Paper Copy (identical to computer copy)
   c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [ ] 37 C.F.R.§3.73(b) Statement (when there is an assignee) [ ] Power of Attorney
10. [ ] English Translation Document (if applicable)
11. [X] Information Disclosure Statement (IDS)/PTO-1449 [X] Copies of IDS Citations
12. [X] Preliminary Amendment
13. [X] Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
14. [ ] * Small Entity Statement(s) (PTO/SB/09-12) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s) (if foreign priority is claimed)
16. [ ] Other: .....

* NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

17. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:
[X] Continuation [ ] Divisional [ ] Continuation-in-part (CIP) of prior application No 08 / 687,329
Prior application information: Examiner K. JORDAN Group / Art Unit: 1614

18. CORRESPONDENCE ADDRESS

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Registration No (Attorney/Agent)	22495
Signature	Eric S. Spector
Date	04/30/98

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FEE TRANSMITTAL

Patent fees are subject to annual revision on October 1.
These are the fees effective October 1, 1997.
Small Entity payments must be supported by a small entity statement, otherwise large entity fees must be paid. See Forms PTO/SB/09-12.
See 37 C.F.R. §§ 1.27 and 1.28.

TOTAL AMOUNT OF PAYMENT ($) 872.00

Complete if Known	
Application Number	TBA
Filing Date	April 30, 1998
First Named Inventor	THOMAS BUSER
Examiner Name	
Group / Art Unit	
Attorney Docket No.	P4947US-WO-A

METHOD OF PAYMENT (check one)

1. [X] The Commissioner is hereby authorized to charge indicated fees and credit any over payments to:

Deposit Account Number: 10-1213
Deposit Account Name: JONES, TULLAR & COOPER, PC

[X] Charge Any Additional Fee Required Under 37 C.F.R. §§ 1.16 and 1.17
[ ] Charge the Issue Fee Set in 37 C.F.R. § 1.18 at the Mailing of the Notice of Allowance

2. [X] Payment Enclosed: (Check #12350)
[X] Check [ ] Money Order [ ] Other

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	790	201	395	Utility filing fee	790
106	330	206	165	Design filing fee	
107	540	207	270	Plant filing fee	
108	790	208	395	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) 790

2. EXTRA CLAIM FEES

	Extra Claims		Fee from below	Fee Paid
Total Claims	16 - 20** =	NONE	X	=
Independent Claims	4 - 3** =	1	X 82	= 82
Multiple Dependent				=

**or number previously paid, if greater; For Reissues, see below

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	22	203	11	Claims in excess of 20
102	82	202	41	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim, if not paid
109	82	209	41	** Reissue independent claims over original patent
110	22	210	11	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 82.00

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet.	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	950	217	475	Extension for reply within third month	
118	1,510	218	755	Extension for reply within fourth month	
128	2,060	228	1,030	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,320	241	660	Petition to revive - unintentional	
142	1,320	242	660	Utility issue fee (or reissue)	
143	450	243	225	Design issue fee	
144	670	244	335	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	50	123	50	Petitions related to provisional applications	
126	240	126	240	Submission of Information Disclosure Stmt	
581	40	581	40	Recording each patent assignment per property (times number of properties)	
146	790	246	395	Filing a submission after final rejection (37 CFR 1.129(a))	
149	790	249	395	For each additional invention to be examined (37 CFR 1.129(b))	

Other fee (specify) _____

Other fee (specify) _____

* Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) -0-

SUBMITTED BY

Typed or Printed Name	ERIC S. SPECTOR	Complete (if applicable) Reg. Number	22495
Signature	[signature]	Date 04/30/98	Deposit Account User ID

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
)
THOMAS BUSER, et al.)
)
Patent Application No. TBA)
)
Filed: April 30, 1998)
)
For: TREATMENT OF INFLAMMATORY BOWEL)
DISEASE USING ORAL DOSAGE FORMS)
OF OMEGA-3 POLYUNSATURATED ACIDS)

PRELIMINARY AMENDMENT

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a preliminary amendment in the continuation of Application No. 08/687,329 filed concurrently herewith.

Please amend the above-identified application as follows:

IN THE SPECIFICATION

Under the title at page 1 insert: --This is a continuation of Application No. 08/687,329, filed on August 7, 1996, the specification of which was described and claimed in PCT International Application No. PCT/EP96/02038, filed on May 13, 1996.--

Page 4, line 15, after "pH.", insert the following sentence: --In the results of the Belluzzi, et al., study, the item before the slash (/) is the pH at which the coating rapidly dissolves and the item following the slash (/) is the time for which the coating is resistant to gastric juice.--

IN THE CLAIMS

Cancel Claims 2, 3, and 6-13.

Amend Claim 4 as follows:

Claim 4, line 1, change "3" to --1--.

Please add the following new claims:

--14. An oral dosage form comprising a coated capsule containing as an active principle an omega-3 polyunsaturated acid in free acid form or a pharmaceutically acceptable salt thereof, characterized in that the coating of the capsule is of a material which dissolves in a time but not pH dependent manner and is resistant to the release of the omega-3 polyunsaturated acid for a period of 30 to 60 minutes at pH 5.5 such that said omega-3 polyunsaturated acid is released in the small intestine.

--15. An oral dosage form as claimed in Claim 14, wherein said acid is eicosapenta-5,8,11,14,17-enoic acid, docosahexa-4,7,10,13,16,19-enoic acid or a mixture thereof.

--16. An oral dosage form a claimed in Claim 14, wherein said acid is present as the sole active principle.

--17. An oral dosage form as claimed in Claim 14, wherein said active principle is an omega-3 polyunsaturated acid in free acid form or a pharmaceutically acceptable salt thereof except for a lithium salt thereof.

--18. An oral dosage form as claimed in Claim 14, wherein the coating comprises iron oxide, titanium dioxide, and talc.

--19. An oral dosage form as claimed in Claim 14, wherein the capsule is a hard or soft gelatin capsule.

--20. An oral dosage form as claimed in Claim 15, wherein the eicosapenta-5,8,11,14,17-enoic acid, docosahexa-4,7,10,13,16,19-enoic acid or mixture thereof is present in an oil constituent in a percentage of at least 60% w/w.

--21. An oral dosage form as claimed in Claim 14 containing as an active principle a unit dose of 250 to 1,000 mg omega-3 polyunsaturated acid.

--22. A method of treating inflammatory bowel disease or reducing clinical relapse thereof, which comprises administering to a patient an effective amount of an oral dosage form comprising a coated capsule containing as an active principle an omega-3 polyunsaturated acid in free acid form or a pharmaceutically acceptable salt thereof, characterized in that the coating of the capsule is of a material which dissolves in a time but not pH dependent manner and is resistant to the release of the omega-3 polyunsaturated acid for a period of 30 to 60 minutes at pH 5.5 such that said omega-3 polyunsaturated acid is released in the small intestine.

--23. A method as claimed in Claim 22, wherein the inflammatory bowel disease is Crohn's disease.

--24. A method as claimed in Claim 23, wherein patients are in clinical remission for less than 24 months prior to treatment.

--25. A method as claimed in Claim 22 which comprises administering a daily dosage of 20 to 50 mg/kg omega-3 polyunsaturated acid.

--26. A method of treating inflammatory bowel disease or reducing clinical relapse thereof, which comprises administering to

a patient an effective amount of an oral dosage form comprising a coated capsule containing as an active principle an omega-3 polyunsaturated acid in free acid form or a pharmaceutically acceptable salt thereof except for a lithium salt thereof, characterized in that the coating of the capsule is of a material which dissolves in a time but not pH dependent manner and is resistant to the release of the omega-3 polyunsaturated acid for a period of 30 to 60 minutes at pH 5.5.--

Remarks

The specification has been amended herewith at page 4, line 15, in the same way as in parent case Application No. 08/687,329.

As a result of the amendment to the claims herein, Claims 1, 4, 5 and 14-26 are in the case.

Claim 1 has been left in for dependency of Claims 4 and 5.

Claims 14-26 are new claims. New Claim 14 is based on allowed Claim 27 in the parent case except that the coating is not limited to a neutral polyacrylate but is described as a material which dissolves in a time but not pH dependent manner. New Claims 15-25 are based on allowed Claims 29, 30, 31, 32, 34, 35, 36 and 38-41 in the parent case but likewise are not limited to a neutral polyacrylate coating. New Claim 26 is the same as claim new Claim 22 except that it excepts lithium salts of omega-3-polyunsaturated acids (as does allowed Claim 31 in the parent case) and except that it does not refer to release location.

Claims 4, 5 and 14-26 are limited to a "time but not pH dependent" capsule coating, i.e., where the capsule coating

material dissolves in the gastrointestinal tract in a time but not pH dependent manner.

Please note that the pH mentioned in Claims 5, 14, 22 and 26 is only a reference pH. This is, this was the pH at which the coating was tested. However, the time dependent coating of the instant invention is resistant for 30 to 60 minutes at any pH of the gastrointestinal tract.

The reference used as a basis of rejection in the parent case was Horrobin U.S. Patent No. 5,422,115 (which is Reference AB in the accompanying Information Disclosure Statement).

The capsule coating of Horrobin does not contemplate a capsule coating which is resistant to dissolving for 30 to 60 minutes at any pH of the gastrointestinal tract.

Horrobin teaches the use of lithium salts to treat Alzheimer's disease. To prevent the lithium salts from dissociating in the pH of the stomach, the oral dosage forms are coated with a gastric juice resistant release coating to carry the capsule through the stomach (column 4, lines 5-9 and column 4, line 59 to column 5, line 12). The obvious enteric coatings for such use are coatings which do not dissolve in the low pH of the stomach but do dissolve in the higher pH of the small intestine. Thus, Horrobin refers to cellulose acetate phthalate (which dissolves at about pH 6.5) and to "Eudragit coating materials." The latter reference means to one skilled in the art a pH dependent Eudragit coating (such as Eudragit L or Eudragit S which are commonly used as enteric coatings for capsules). This is because the term "gastric juice resistant" which Horrobin uses (column 4, lines 8, 9; column 4,

line 62; column 5, lines 3-4) connotes pH dependency to one skilled in the art and because Horrobin defines the term "enteric coating" as meaning a gastric juice resistant coating (column 5, lines 3-4). On the other hand, Eudragit NE 30D, as used in the present invention, is an example of a material whose dissolution is controlled only by time in the gastrointestinal tract but not pH, and to the inventors' knowledge has never before been used as an enteric coating for a liquid containing capsule. Thus, contrary to the contention in the final Office Action of 12 December 1997 in the parent case, Horrobin does not suggest the particular type of acrylate coating contemplated by the instant invention (i.e., Horrobin does not contemplate the use of time dependent capsule coating to control release of the capsule contents) but rather suggests to those skilled in the art "Eudragit coating materials" which dissolve on a pH dependent basis.

New Claim 17 is yet a further step removed from Horrobin since it excludes lithium salts of omega-3 polyunsaturated acids and the whole point in Horrobin is lithium therapy.

Claims 22-26 are also further removed from Horrobin since they relate to the treatment or reducing clinical relapse of inflammatory bowel disease; and Claim 24 is further removed in reciting reducing clinical relapse of Crohn's disease wherein the patients are in remission for less than 24 months (i.e., high relapse period) prior to treatment. Although Horrobin mentions Crohn's disease and ulcerative colitis at column 1, line 35 and column 1, lines 42/43, and column 4, line 33, effective teaching of the patent to a man skilled in the art <u>with respect to coatings on</u>

dosage forms of lithium salts of polyunsaturated fatty acids is with respect to treating Alzheimer's disease as is indicated by the claims in the patent and by column 4, lines 5-9 and column 4, line 59 - column 5, line 12 of the patent. Furthermore, independent method Claim 26 is far removed from any teaching in Horrobin as it excludes lithium salts and the context of Horrobin is lithium therapy.

An Information Disclosure Statement is submitted herewith which cites the documents of record in the parent application.

Allowance is requested.

Respectfully submitted,

JONES, TULLAR & COOPER, P.C.

By: 

Eric S. Spector
Reg. No. 22,495

JONES, TULLAR & COOPER, P.C.
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April 30, 1998

Case P4947US-WO-A

TREATMENT OF INFLAMMATORY BOWEL DISEASE USING ORAL DOSAGE FORMS OF OMEGA-3 POLYUNSATURATED ACIDS

The present invention relates to the oral administration of omega-3 polyunsaturated acids especially, but not exclusively, eicosapenta-5,8,11,14,17-enoic acid ("EPA") and/or docosahexa-4,7,10,13,16,19-enioc acid ("DHA"). In particular, it provides enteric dosage forms of omega-3 polyunsaturated acids for the treatment of inflammatory bowel disease especially, but not exclusively, Crohn's disease and ulcerative colitis.

It is known that DHA, EPA and other omega-3 polyunsaturated acids are of use in the treatment of inflammatory bowel disease (see, for example, EP-A-0244832, EP-A-0289204, EP-A-0311091 & WO-A-93/21912).

EP-A-0244832 discloses pharmaceutical compositions containing certain unsaturated fatty acids with certain specified stimulators. The compositions are of use for treating disorders associated with prostaglandin deficiency, especially gastrointestinal ulcers. The unsaturated fatty acids are those which have 3 to 5 isolated double bonds and 18 to 22 carbon atoms arranged in a straight chain and are capable of being methylated or ethylated at one or two carbon atoms in positions 2, 3, 4, 16, 17, 18, 19 or 20. EPA is amongst the exemplified acids. Reference is made to pH dependent delayed release formulations containing polystyrene or polyacrylic derivatives and to enteric coated products.

EP-A-0289204 discloses disinfectant and pharmaceutical compositions comprising the lithium salt of a C_{18}-C_{22} polyunsaturated fatty acid. Specified polyunsaturated fatty acids include DHA and EPA. The pharmaceutical

compositions can be for enteral, parenteral and topical administration and are for use in the treatment of conditions responsive to lithium and/or polyunsaturated fatty acid therapy. Specified conditions responsive to polyunsaturated fatty acid therapy include Crohn's disease and ulcerative colitis. Reference is made to providing an enteric coat of, for example, an acrylate or cellulose acetate phthalate to delay release of the salt until the intestine.

EP-A-0311091 discloses physiologically acceptable isotonic fat emulsions containing an omega-3-fatty acid or ester, a medium-chain length triglyceride, and an emulsifier. The fatty acid or ester component can be present as a pure compound or in the form of a fish oil and preferably is EPA. The emulsion is administered parenterally for, inter alia, treatment of chronic inflammatory bowel disease.

WO-A-93/21912 discloses the use of emulsions containing a polyunsaturated long-chain omega-3-fatty acid or ester for parenterally administration to treat inflammatory disorders including inflammatory bowel disease. The fatty acid or ester can be present as fish oil and preferred fatty acids include DHA and EPA.

Enteric coated products containing DHA or EPA have been reported for use in the treatment of other conditions (see EP-A-0336662, GB-A-2090529, JP-A-62201823, & WO-A-90/04391)

EP-A-0336662 discloses the microencapsulation of fish oil acids within an enteric coating to provide a stable, odorless and tasteless composition for incorporation into a food product to reduce plasma triglyceride, low density lipoprotein and cholesterol levels . The specified coating

materials are ethyl cellulose, cellulose acetate phthalate and cellulose acetate trimelitate. Reference is made to release of the active below the pylorus in the upper portion of the intestine but there is no specific reference to targeting release to the ileum.

GB-A-2090529 discloses the prophylaxis and treatment of thrombosis using DHA or esters or amides thereof. Reference is made in general terms to intestine soluble coated tablets and to film coated tablets.

JP-A-62201823 discloses enterically coated capsules for treating enteral abnormal fermentation or diarrhoea which contain bacteria in an oil. The oil can be EPA and a number of enteric materials are specified including shellac, carboxymethyl cellulose, cellulose acetate phthalate, hydroxymethyl propylcellulose phthalate, and polyvinyl alcohol phthalate.

WO-A-90/04391 (and corresponding GB-A-2223943) discloses that enteric dosage forms of EPA, DHA and other omega-3 polyunsaturated fatty acids overcome the problem of belching and flatulence associated with oral administration of these acids. The exemplified coating is cellulose acetate phthalate/ethyl phthalate but reference is made to the use of polymethacrylate as the coating material.

Belluzzi et al (Dig. Dis. Sci. 39 (1994) 2589-2594) reported a study in which five groups of patients with Crohn's disease were treated with:-

Group A - uncoated gelatine capsules containing 500 mg "Purepa" fish oil concentrate (containing EPA 40% and DHA 20%);

Group B - gelatine capsule containing 500 mg "Purepa" fish oil concentrate and coated with a pH 5.5/120 minutes or cellulose acetate

trimellate ("CAT") coating;

Group C - gelatine capsule containing 500 mg "Purepa" fish oil concentrate and coated with a pH 5.5/60 minutes CAT coating;

Group D - gelatine capsule containing 500 mg "Purepa" fish oil concentrate and coated with a pH 6.9/120 minutes cellulose acetate phthalate ("CAP") coating; and

Group E - uncoated gelatine capsule containing 1000 mg "Max-EPA" triglyceride fish oil (EPA 18% and DHA 10%).

CAP dissolves at pH 6.8 and CAT dissolves at pH 5.5. All the coated capsules disintegrate within 15 minutes at the relevant pH.

The four groups taking Capsule Types A to D took 9 capsules (2.7 g of omega-3 polyunsaturated acid) during meals 3 times daily for 6 weeks and those taking Type E capsules received 12 capsules (3.4 g of omega-3 polyunsaturated acid) daily in divided doses during meals over the 6 week period.

All of the five regimens increased the incorporation of the omega-3 polyunsaturated acid both in plasma and red blood cell phospholipid membranes by displacing arachidonic acid, linoleic acid, and to a lesser extent oleic acid. However, much more of the free omega-3 polyunsaturated fatty acid mixture was absorbed using the capsules containing "Purepa" fish oil concentrate than when using "Max-EPA" triglyceride mixture. The incorporation was coating dependent and it is speculated to be related to the site of capsule-disintegration. The Group C capsules (having the pH 5.5/60 minutes coating) gave the best incorporation of the omega-3 polyunsaturated fatty acids in the plasma and red blood cell phospholipid membranes. The

Group D capsules (having the pH 6.9 coating) gave very poor incorporation and 70% of patients in this Group had increased daily bowel motion. Slightly better incorporation was registered with the Group B capsules (having the pH 5.5/120 minutes coating), but 50% of 5 patients in the Group reported diarrhoea.

The Group C capsules used by Belluzzi et al combined both pH and time-dependent release mechanisms and made it possible to avoid capsule-breakdown (pH 5.5) in the stomach-duodenum, and consequently void upper gastro-intestinal side-effects. Since they were only gastric resistant for 60 minutes, they allowed quick release of the fish oil concentrate in the small intestine and its complete absorption.

Surprisingly, it has now been found that the optimum combination of absorption and absence of side effects occurs if the release of polyunsaturated fatty acid is controlled to occur in the ileum, especially mid-ileum.

Thus, the present invention provides an oral dosage form, containing as an active principle an omega-3 poly-unsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof, which releases the acid in the ileum.

The present invention also provides the use of an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof in the manufacture of a medicament releasing the acid in the ileum for the treatment of inflammatory bowel disease.

Further, the present invention provides the use of said oral dosage forms in the treatment inflammatory bowel disease.

It is preferred that the omega-3 polyunsaturated acid is DHA, EPA or a mixture thereof. It is present in free acid form or as a pharmaceutically acceptable salt thereof and can be present as the sole active principle or with other active principles. Suitably, a fish oil concentrate containing at least 60% by weight DHA and EPA is used.

Omega-3 polyunsaturated acids are readily oxidised and hence an antioxidant usually will be present. The presently preferred antioxidant is gamma-tocopherol but other pharmacologically acceptable antioxidants can be used, for example butylated hydroxy anisole, butylated hydroxy toluene, propyl gallate or a quinone.

The oral dosage form may also contain one or more pharmaceutically acceptable excipients depending upon the precise nature of the dosage form. Suitably, the oral dosage form can be a coated tablet containing the omega-3 polyunsaturated acid in a microencapsulated form or loaded on a suitable absorbent. However, it is preferred that the oral dosage form is a coated capsule, especially a soft or, more especially, hard gelatine capsule.

The coating must be such as to release the acid in the ileum, preferably in the mid-ileum. Usually, dissolution of the coating will be entirely time dependent but a coating relying on a combination of time and pH dependence can be used. Suitably, the coating is resistant for a period of 30 to 60 minutes at pH 5.5. The presently preferred coating is a neutral polyacrylate such as a poly(ethylacrylate-methylmethacrylate), especially Eudragit NE 30-D (Röhm Pharma GmbH) which has an average molecular weight of about 800,000.

Usually, the omega-3 polyunsaturated acid will be administered in a daily dosage of 20 to 50 mg/kg,

especially 30-40 mg/kg. The actual dose will vary depending inter alia on the identity of the omega-3 polyunsaturated acid and the nature and degree of the disorder being treated. Usually, each unit dose will contain 250 to 1000 mg, especially 400 to 800 mg.

The following is a description, by way of example only, of a presently preferred embodiment of the invention.

Example 1

Transparent hard gelatine capsules (Elanco Qualicaps size 0; Lilly France SA) were each filled with 500 mg of a fish oil concentrate containing at least 60% by weight DHA and EPA (Incromega 3F60; Croda Universal Ltd, UK). The filled gelatine capsules were film coated with Eudragit® NE 30-D to provide resistance for 30 to 60 minutes at pH 5.5 by spraying with a film coating composition (see below) at 35 ml/min using 0.8 bar pressure at 25°C and air drying for at least 30 mins at 25°C.

The film coating composition (for 50,000 capsules) was prepared by slowly adding silicon anti-foam emulsion (0.36 mg), brown iron oxide (E 172; 3.00 mg), titanium dioxide (2.35 mg) and talc (10 mg) in succession to water (75 mg) and agitating for 1 to 2 hours to form a very fine dispersion. A 30% aqueous dispersion of a poly(ethyl-acrylate-methylmethacrylate) having an average molecular weight of about 800,000 (Eudragit® NE 30D; 60 mg) and added to polysorbate 80 (MO 55 F; 0.2 mg) in a little water and the resultant mixture agitated. Silicon anti-foam emulsion (2 or 3 drops) was added to destroy the resultant foam and the aforementioned dispersion was slowly added. The vessel was washed with water (25 mg) and the dispersion stirred for 30 minutes before being filtered (150 μm).

Example 2

A double-blind placebo-controlled randomised study was conducted using 78 patients with well established diagnosis of Crohn's disease in clinical remission according to the Crohn's disease activity index (CDAI) and satisfying all the following criteria:-

(a) CDAI <150 for at least 3 months but less than 2 years;
(b) at least one abnormal value of alpha-1 acid glycoprotein (>130 mg/d]), erythrocyte sedimentation rate (ESR);
(c) (>40mm/h), or alpha-2 globulin (>0,9 g/dl);
(d) no treatment with 5-aminosalicylate, suiphasalazine or corticosteroids in the previous 3 months, or with immunosuppressive therapy in the previous 6 months;
(e) no previous bowel resection >1 m; and
(f) age 18-75 years.

The patients were blindly randomised into two groups of 39 patients to receive daily either 9 enteric-coated hard gelatine capsules containing 500 mg of a fish oil concentrate ("Purepa"; see Table 1) or 9 enteric-coated capsules of identical appearance containing 500 mg of a placebo (Miglyol® 812). The fish oil concentrate contained 40% EPA and 20% DHA. Both sets of capsule were coated with Eudragit NE 30D to resist gastric acid or gut juice for at least 30 min and to disintegrate within 60 min at pH 5.5, allowing release of the fish oil in the small intestine. During the treatment the patients did not take any other medication. The clinical characteristics of both groups of patient are set forth in Table 2.

Table 1

COMPOSITION OF CAPSULE CONTENTS

	Purepa (fish oil)	Miglyol (placebo)
Lipid profile	Free fatty acids %	Neutral oil
C 14:0	-	
C 16:0	0.4	
C 16:1	3.2	
C 16:2	2.1	
C 16:3	2.4	
C 16:4	5.2	
C 18:0	-	
C 18:1	0.8	
C 18:2	1.5	
C 18:3	1.3	
C 18:4	6.9	
C 20:1	-	
C 20:3	1.5	
C 20:4 (AA)	1.7	
C 20:5 (EPA)	42.4	
C 21:5	1.6	
C 22:5	0.5	
C 22:6 (DHA)	19.9	

Table 2

CLINICAL CHARACTERISTICS OF PATIENTS

	PUREPA	PLACEBO
MALE	20	19
FEMALE	19	20
AGE (years; median (range)	34 (18-67)	39 (20-65)
SMOKERS	14/39	13/39
DURATION OF DISEASE (months, median (range)	68 (24-94)	66 (20-88)
PREVIOUS OPERATION < 1m	14/39	13/39
SITE OF INVOLVEMENT		
ileum	25	24
ileum + colon	14	15
CDAI median (range)	78 (28-120)	82 (30-112)
ESR (mm/h)	36.9 (SD 27-min 6;max 122)	35.7 (SD 24-min 12;max 90)
ALPHA-2 globulins (g/l)	9.6 (SD 1.8-min 6.1;max 13.2)	9.2 (SD 1.3-min 6.5;max 11.9)
ALPHA-1 GLYCOPROTEIN (mg/dl)	136.8 (SD 52-min 53;max 257)	137.1 (SD 58-min 60;max 263)

Each patient in the fish oil group received 1.8 g of EPA and 0.9g of DHA daily for 12 months. They were examined on entry to the study and at 3, 6 and 12 months or before if symptoms worsened with an increase of CDAI of at least 100 points from baseline value and above 150 for more than 2 weeks. During each visit, laboratory tests were made of blood, kidney, liver, ESR, alpha-1 acid glycoprotein, alpha-2 globulin and CRP (c-AMP-Receptor-Protein). At time 0, 6 months and at the end of the study, 2 ml of packed red cells and polymorphonuclear leucocytes were obtained following the procedure described by Popp-Snijders et al (Scan. J. Clin. Lab. Invest 44 (1984) 39-46) and their membrane lipids were extracted as described by Dodge and Phillips (J. Lipid Res. 8 (1967) 667-675) using a 2:1 mixture of chloroform and methanol containing 0.01% butylated hydroxytoluene (2,6 di-tert-butyl-p-cresol) as antioxidant. Samples were stored under nitrogen at -20°C for less than 2 weeks prior to separation of the phospholipids and analysis of the omega-3 polyunsaturated fatty acids. Phospholipid fractions were obtained from the extracted lipids using 1-dimensional thin layer chromatography. The samples were spotted in one corner of a silica plate and developed with chloroform/methanol/acetic acid/water (25:14:4:2). The separated phospholipids were transmethylated using 1 N potassium hydroxide in methanol and boron trifluoride in 14% methanol for 10 min at 80°C. Fatty acid methyl esters were then extracted in hexane, resuspended in 100 µl of benzene and analyzed by gas-chromatography equipped with a capillary column (0.32 mm i.d. x 25 m), using helium as the carrier gas (flow rate 3ml/min) and flame ionisation detection. The column temperature was programmed between 170°C and 210°C at 5°/min with the injector and detector temperatures at 220°C and 250°C, respectively. Individual fatty acid methyl esters were identified by comparison with commercial

standards. Heptadecanoic acid (17:0) was used as the internal standard (1 mg/ml in benzene) and the results expressed as relative percentages.

The difference in the relapse rate in the fish oil and placebo groups was analyzed using the chi-squared test on a 'compliance only' and 'intention to treat' basis. Differences between features of patients in the active and the placebo group were analyzed using the Mann-Whitney U-test, and the laboratory results were analyzed with Student's t-test for paired data (both tests 2-tailed). Kaplan-Maier life-table curves for patients remaining in remission were calculated according to the assigned treatment. Differences in the curves were tested by log rank analysis. Multiple regression analysis was performed between some variables (trial treatment, gender, age, previous surgery, length of disease) and clinical relapses; the forward procedure was used for selecting a more representative model.

In the fish oil group, 1 patient withdrew (moved away) and 4 dropped out because of diarrhoea. In the placebo group, 1 patient withdrew (did not attend the outpatient clinic) and 1 dropped out because of diarrhoea. Diarrhoea started in all 5 cases within the first month of treatment and symptoms did not improve when the daily capsule intake was reduced. This diarrhoea might have been due to the delivery of the capsule contents into the distal part of the gut. The coating is time-dependent (30-60 min at pH 5.5) so if the transit time is short, the capsules would remain intact further along the intestine.

The relapse rate was significantly reduced by the fish oil compared to the placebo group: chi squared 11.75; p=0.0004 (difference 41%, 95% confidence interval (Cl) 16-

66). This difference was significant too on an intention to treat analysis: chi squared 9.05; p=0.0026 (difference 32%, 95% (Cl) 12-52).

Table 3 summarises the clinical results and Table 4 summarises the laboratory variables of inflammation at entry and at 12 months in the patients who received the fish oil and were still in remission at the end of the study. No significant decrease in any of the laboratory findings of disease activity occurred in the placebo group. Table 5 shows the incorporation of the main fatty acids into phospholipid membranes (AA = arachidonic acid and LA = linoleic acid). Multiple regression analysis indicated that only the fish oil capsules significantly affected clinical relapse (t=3,16; p=0,002;F ratio=10; p=0,002).

Over a period of 12 months the fish oil capsules used in the study reduced the clinical relapse of Crohn's disease in comparison with placebo by 50%. It is important to note that the patients in the study were in clinical remission for less than 24 months prior to entry, and presented laboratory evidence of inflammation. Patients of this type have about 75% greater risk of relapse in comparison with patients with long previous remission with normal laboratory tests.

The results indicate that the fish oil capsules are the most effective and safe available treatment for preventing clinical relapses in Crohn's disease, with relatively few side effects.

Table 3

CLINICAL RESULTS AFTER 12 MONTHS OF TREATMENT

	fish oil (n=39)	placebo (n=39)
Withdrew	1	1
REMISSIONS	23/38	10/38
drop-out	4	1
RELAPSES (intention to treat) with drop out	15/38 (39,5%)*	28/38 (73,7%)
	*chi square 9.05; p = 0.0026	
excluding drop-outs	11/34 = 32,4%	27/37 = 73,0%
	*chi square 11,75; p = 0.0004	

Table 4

23 PATIENTS GIVEN PUREPA IN REMISSION AFTER 12 MONTHS

	TIME 0	12 MONTHS
ESR (mm/h)	37.8(6-122)SD 25	19.5(3-40)SD 11.2
	p= 0.0002	
CRP (mg/dl)	3.6(0.2-9.9)SD 3.4	1.0(0.2-3.5)SD 0.9
	p= 0.001	
ALFA-2 GLOBULIN (G/DL)	0.91(0.64-1.32)SD 0.15	0.74(0.56-0.91)SD 0.1
	p= 0.001	
ALFA-1 GLYCOPROTEIN (mg/dl)	137(57-248)SD 49	111(69-180)SD 33
	p= 0.002	
ALBUMIN (g/dl)	3.7(3.0-4.4)SD 0.4	4.0(3.1-4.7)SD 0.35
	p= 0.004	
WBC	8780(4000-11700)SD 2093	7400(3310-11550)SD 2634
	p= 0.01	

Table 5

PERCENTAGE OF MAIN FATTY ACIDS INCORPORATED INTO RBCs

	PUREPA			MIGLYOL		
	TIME 0		6 MONTHS	TIME 0		6 MONTHS
18:2n-6 LA	10.2±1	7.0±0.8	6.4±0.4	10.6±1.5	9.8±2	11.1±1.5
20:4n-6 AA	13.9±1.5	8.4±1.2	7.1±1.2	13.5±1.3	12.3±1.8	14.1±1.2
20:5n-3 EPA	0.2±0.1	4.1±0.3	5.8±0.6	0.3±0.1	0.1±0.1	0.2±0.1
22:6m-3 DHA	2.9±0.6	7.4±1.2	11.4±1.2	3.2±0.5	2.8±0.7	3.0±0.6

CLAIMS

1. An oral dosage form containing as an active principle an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof, characterized in that it releases the acid in the ileum.

2. An oral dosage form as claimed in Claim 1, wherein the omega-3 polyunsaturated acid is released in the mid-ileum.

3. An oral dosage form as claimed in Claim 1 or Claim 2, wherein release of the omega-3 polyunsaturated acid is controlled by an exterior coating on a capsule containing the said active principle.

4. An oral dosage form as claimed in Claim 3, wherein delay in dissolution of the coating is time-dependant but not pH dependent.

5. An oral dosage form as claimed in Claim 4, wherein the coating is resistant for a period of 30 to 60 minutes at pH 5.5.

6. An oral dosage form as claimed in Claim 4 or Claim 5, wherein the coating is a neutral polyacrylate.

7. An oral dosage form as claimed in Claim 6, wherein the coating is a poly(ethylacrylate-methylmethacrylate).

8. An oral dosage form as claimed in any one of the preceding claims, wherein said acid is DHA, EPA or a mixture thereof.

9. An oral dosage form as claimed in any one of the preceding claims, wherein said acid is present as the sole active principle.

10. The use of an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof in the manufacture of a medicament releasing the acid in the ileum for the treatment of inflammatory bowel disease.

11. A use as claimed in Claim 13, wherein the medicament is an oral dosage form as defined in any one of Claims 2 to 9.

12. The use of an oral dosage form as claimed in any one of Claims 1 to 9 in the treatment of inflammatory bowel disease.]

13. A method of treating inflammatory bowel disease, which comprises administering to a patient an effective amount of an oral dosage form as claimed in any one of Claims 1 to 9.

ABSTRACT

TREATMENT OF INFLAMMATORY BOWEL DISEASE USING ORAL DOSAGE FORMS OF OMEGA-3 POLYUNSATURATED ACIDS

Inflammatory bowel disease, especially Crohn's disease and ulcerative colitis, is treated by administration of an oral dosage form, containing as an active principle an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof, which releases the acid in the ileum. Preferably the oral dosage form is a gelatine capsule coated with a poly(ethylacrylate-methyl-methacrylate).

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed for and for which a patent is sought on the invention entitled:

TREATMENT OF INFLAMMATORY BOWEL DISEASE USING ORAL DOSAGE FORMS OF OMEGA-3 POLYUNSATURATED ACIDS

the specification of which:

[X] is attached hereto.

[ ] was filed on _____ as Application Serial No._____ and was amended on _____.

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Sec. 1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, Sec. 119, of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent of inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

9509764.8	GB	15 May 1995	[X] Yes	[ ] No
(Number)	(Country)	(day/month/year filed)		
_____	_____	_____	[ ] Yes	[ ] No
(Number)	(Country)	(day/month/year filed)		

I hereby claim the benefit under Title 35, United States Code, Sec. 120 of any United States application(s) listed below, and insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Sec. 112, I acknowledge the duty to disclose material information

as defined in Title 37, Code of Federal Regulations, Sec. 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

PCT/EP96/02038	13 May 1996	Pending
(Application Serial No.)	(Filing Date)	(patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(patented, pending, abandoned)

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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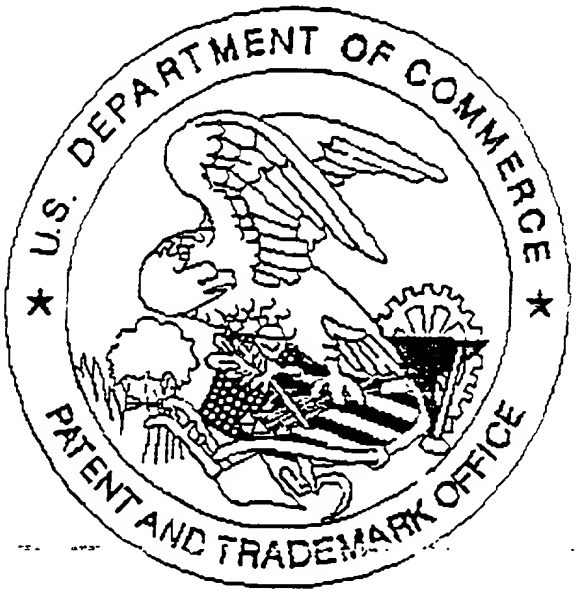

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